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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/765,668	01/27/2004	David B. Rozema	Mirus.042.02	9890

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EXAMINER	
DUNSTON, JENNIFER ANN	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 09/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/765,668	ROZEMA ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2006 and 19 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,7,8,12-14,16 and 17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,7,8,12-14,16 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/23/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the amendment, filed 6/19/2006, in which claims 1-4, 6, 9-11, 15 and 18-20 were canceled; and claims 5, 7, 8, 12-14, 16 and 17 were amended. Currently, claims 5, 7, 8, 12-14, 16 and 17 are pending and under consideration. Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

Information Disclosure Statement

Receipt of an information disclosure statement, filed on 1/23/2006, is acknowledged. The signed and initialed PTO 1449 has been mailed with this action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7 and 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This is a new rejection, necessitated by the amendment of claim 7 in the reply filed 6/19/2006.

Claim 7 is vague and indefinite in that it depends from a canceled claim, claim 1. Claim 1 was drawn to a product; however, claim 7 is drawn to "the process of claim 1." Accordingly,

the metes and bounds of the method are wholly unclear. It would be remedial to amend the dependency such that the claim further limits a pending claim.

Claim 8 depends from claim 7 and is indefinite for the same reasons as applied to claim 7.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5, 12-14, 16 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the delivery of a polynucleotide to the cytoplasm of a cell *in vitro*, does not reasonably provide enablement for the delivery of a polynucleotide to a cell *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This is a new rejection, necessitated by the amendment of claims in the reply filed 6/19/2006.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The claims are drawn to methods of delivering a polynucleotide to the cytoplasm of a cell. The claims read on the delivery of the polynucleotide to a cell in

culture or a cell within an organism (i.e. gene therapy). Claims 5, 7 and 8 require the polynucleotide to be delivered by a styrene-maleic anhydride-based random copolymer with hydrophobic groups covalently linked to the anhydride monomers. Claims 12-14, 16 and 17 require the polynucleotide to be delivered by a vinyl ether-maleic anhydride-based alternating copolymer with hydrophobic groups covalently linked to the anhydride monomers. With respect to gene therapy applications, the nature of the subject matter is complex, because the nucleic acid must be delivered at a level sufficient to produce a therapeutic outcome (see the discussion below).

Breadth of the claims: The claims are broad in that the read on the delivery of polynucleotides *in vitro* and *in vivo*. The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims.

Predictability and state of the art: An analysis of the prior art as of the effective filing date of the present application shows the complete lack of documented success for any treatment based on gene therapy. In a review on the current status of gene therapy, both Verma et al (Nature, Vol. 389, pages 239-242, 1997; e.g. page 239, paragraph 1) and Palù et al (J. Biotechnol. Vol. 68, pages 1-13, 1999; e.g. Abstract) state that despite hundreds of clinical trials underway, no successful outcome has been achieved. The continued, major obstacles to successful gene therapy are gene delivery and sustained expression of the gene. Regarding non-viral methods for gene delivery, Verma et al indicate that most approaches suffer from poor efficiency and transient expression of the gene (e.g. page 239, right column, paragraph 2). Likewise, Luo et al (Nature Biotechnology, Vol. 18, pages 33-37, 2000) indicate that non-viral synthetic delivery systems are very inefficient (e.g. Abstract; page 33, left column, paragraphs 1

and 2). Regarding viral methods for gene delivery *in vivo*, Verma et al, indicate that lentiviral, adenoviral and AAV vectors are capable of delivery genes, but there is a possibility for insertional mutagenesis or toxicity due to an inflammatory response (e.g. Table 2).

As discussed above, the method of *in vivo* gene therapy is highly complex and unpredictable due to the poor efficiency of the delivery of the polynucleotide and transient expression of the polynucleotide. Indeed, recent gene therapy protocols have demonstrated unpredictable outcomes resulting from an unexpected inflammatory reaction to an adenoviral vector in a patient and the insertional mutagenesis of a gene resulting in a leukemia-like condition in children being treated for severe combined immunodeficiency (Edelstein et al, J. Gene Med. Vol. 6, pages 597-602, 2004; e.g. page 599, The hopes and the setbacks). The skilled artisan at the time the present invention was made recognized the difficulty of achieving sufficient heterologous gene expression to induce any therapeutic effect.

Guidance of the specification and existence of working examples: The specification envisions using homopolymers, random copolymers or alternating copolymers that are maleic anhydride-based anionic polymers containing hydrophobic groups for the delivery of biologically active compounds to cells *in vivo* or *in vitro* (e.g. page 3, lines 7-21). The specification teaches that the polymers are easily synthesized from commercially available monomers and can be easily reacted with alcohols and/or amides to form esters and/or amides (e.g. paragraph bridging pages 5-6). For *in vivo* applications, the specification envisions the administration of the polymer and biologically active compound by intravascular, intramuscular, intraparenchymal, intradermal, subdermal, subcutaneous, intratumor, intraperitoneal, etc.

With respect to polynucleotides, the specification indicates that the term encompasses

DNA, RNA, and combinations of DNA, RNA and other natural and synthetic nucleotides (e.g. page 9, lines 14-29). The specification envisions the delivery of a polynucleotide to a cell to express an exogenous nucleotide sequence, to inhibit, eliminate, augment, or alter expression of an endogenous nucleotide sequence, or to affect a specific physiological characteristic not naturally associated with the cell (e.g. page 10, lines 1-3). Inhibitors envisioned by the instant specification include siRNA, microRNA, interfering RNA, RNAi, dsRNA, ribozymes, antisense polynucleotide, and DNA expression cassettes encoding the aforementioned RNA molecules (e.g. page 10, lines 5-23).

The working examples of the specification are all directed to the transfer of polynucleotides into cells *in vitro*. No working examples are provided for any *in vivo* embodiment.

Amount of experimentation necessary: The quantity of experimentation necessary to carry out the claimed invention is high, as the skilled artisan could not rely on the prior art or the present specification to teach how to make and use the claimed methods commensurate in scope with the claims. With any nucleic acid one would have to determine how to deliver the given nucleic acid to the appropriate target cells with specificity and efficiency, and how to get sufficient expression to induce at least some therapeutic effect. Since neither the prior art nor the specification provides the answers to all of these questions, it would require a large quantity of trial and error experimentation by the skilled artisan to do so. Considering the unpredictable nature of gene therapy, the type of experimentation required is not routine, and the amount of experimentation is undue.

In view of the breadth of the claims and the lack of guidance provided by the

specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claims 5, 12-14, 16 and 17 are not considered to be fully enabled by the instant specification.

Response to Arguments - 35 USC § 112

The previous rejection of claims 6-8 and 13-17 under 35 U.S.C. 112, second paragraph, has been withdrawn in view of Applicant's amendment to the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 12, 13, 16 and 17 are rejected under 35 U.S.C. 102(e) as being anticipated by Rozema et al (US Patent Application Publication No. 2002/0052335; see the entire reference). This is a new rejection, necessitated by the amendment of claims in the reply filed 6/19/2006.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the

inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Regarding claim 12, Rozema et al teach a method for delivering a nucleic acid to a cell, comprising the steps of (i) forming poly(methylvinylether maleic anhydride), pMVMA, (ii) reacting the pMVMA with an amine-containing compound, such as histamine to form pMVMA with hydrophobic imadzole groups linked to the anhydride monomers in the copolymer, Mirus Corporation number 510 (MC510), (iii) mixing MC510, a polycation and a nucleic acid, and (iv) contacting a cell or organism with the MC510/nucleic acid complex (e.g. paragraphs [0035], [0087] and [0122]-[0129]).

Regarding claim 13, the methyl vinyl ether of the MC510 compound is an alkyl vinyl ether (e.g. paragraph [0123]).

Regarding claim 16, the reaction of the histamine will form a hydrophobic ester group (e.g. paragraphs [0122]-[0126]).

Regarding claim 17, the histamine linked to the anhydride monomer of the polymer is a functional group (e.g. paragraphs [0122]-[0128]). Furthermore, Rozema et al teach the introduction of functional groups, such as targeting groups, to the polymer monomers before or after polymerization (e.g. paragraph [0058]).

Claims 12, 13, 16 and 17 are rejected under 35 U.S.C. 102(e) as being anticipated by Trubetskoy et al (US Patent No. 6,740,336; see the entire reference), as evidenced by Rozema et al (US Patent Application Publication No. 2002/0052335). This is a new rejection, necessitated by the amendment of claims in the reply filed 6/19/2006.

Trubetskoy et al teach a method of introducing a nucleic acid into a cell, comprising the steps of (i) forming a complex by mixing DNA with 1PEI and adding MC510 to the binary complex, and (ii) adding the complex to cells cultured *in vitro* (e.g. column 12, lines 35-56). Rozema et al is cited only to show that MC510 is made by forming poly(methylvinylether maleic anhydride), pMVMA and reacting the pMVMA with histamine to form pMVMA with hydrophobic imadzole groups linked to the anhydride monomers in the copolymer, Mirus Corporation number 510 (MC510) (e.g. paragraphs [0035] and [0122]-[0129]). The methylvinylether is an alkyl vinyl ether, and the histamine linked to the maleic anhydride monomers forms a hydrophobic ester, which is a functional group.

Response to Arguments - 35 USC § 102

The previous rejection of claims 5-8 under 35 U.S.C. 102(b) as being anticipated by Maeda et al (US Patent No. 4,732,933) as evidenced by Maeda et al (Journal of Controlled Release, Vol. 74, pages 47-61, 2001) has been withdrawn in view of Applicant's amendment to the claims.

The previous rejection of claims 5-8 under 35 U.S.C. 102(b) as being anticipated by Maeda et al (Journal of Controlled Release, Vol. 74, pages 47-61, 2001) has been withdrawn in view of Applicant's amendment to the claims.

The previous rejection of claims 5 and 12-14 under 35 U.S.C. 102(e) as being anticipated by Tonge et al has been withdrawn in view of Applicant's amendment to the claims.

The previous rejection of claims 12-17 under 35 U.S.C. 102(b) as being anticipated by Saettone et al has been withdrawn in view of Applicant's amendment to the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 5, 12-14, 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tonge et al (US Patent No. 6,436,905, cited in a prior action; see the entire reference) in view of Maeda et al (US Patent No. 4,732,933, cited in a prior action; see the entire reference). This is a new rejection, necessitated by the amendment of claims in the reply filed 6/19/2006.

Tonge et al teach a composition comprising a synthetic amphipathic polymer, including both hydrophobic groups and anionic hydrophilic groups and acting as a lipid-solubilizing agent (e.g. column 3, lines 49-52). Tonge et al teach that especially suitable polymers may be formed as alternating copolymers of maleic acid (or the anhydride thereof) with styrene, indene or a C_{1-4} alkyl, e.g. methyl substituted styrene or indene, or with propyl (or isopropyl) or butyl vinyl ether

(e.g. column 6, lines 27-31, 60-63). Tonge et al disclose examples of suitable polymers, including Poly(maleic anhydride-styrene) (a random copolymer), Poly(maleic anhydride-propyl vinyl ether), and Poly(maleic anhydride-butyl vinyl ether) (e.g. column 6, lines 60-63). Tonge et al teach the use of the polymers to administer drugs or DNA or RNA to cells to facilitate the uptake of the therapeutic agent into target cells (e.g. column 1, lines 31-45; column 12, line 40 to column 13, line10).

Tonge et al do not teach covalently linking hydrophobic groups to anhydride monomers in the copolymer. Tonge et al do not teach the formation of hydrophobic esters of the alkyl vinyl ether maleic anhydride copolymers or styrene maleic anhydride copolymers.

Maeda et al teach half-esterified styrene-maleic anhydride copolymers (SMA) for the delivery of the antitumor drug neocarzinostatin (NCS) to cells (e.g. column 4, lines 4-10; column 3, lines 25-47). Maeda et al teach the reaction of the maleic acid units to form hydrophobic esters of a monohydric alcohol or a monohydroxyalkyl ether of a di- or trihydric alcohol (e.g. column 1, lines 20-46). One embodiment disclosed by Maeda et al is neocarzinostatin-half butyl-esterified styrene-maleic acid copolymer complex (SMANX) (e.g. Example 1). Maeda et al teach the administration of the copolymer complex to tumor cells *in vivo* (e.g. paragraph bridging columns 6-7; column 3, lines 55-65). The compound is capable of entering the cell as evidenced by the effect of SMACS complex *in vivo* on the surviving percentage of mice with tumor cells implanted in the abdominal cavity (e.g. column 11, lines 58-68; column 12, lines 28-33; Table 6). Maeda et al teach that the addition of the half-esterified residues provides the advantage of providing lipid solubility while maintaining water solubility, which allows the

composition to be administered as a water soluble composition (e.g. column 3, line 66 to column 4, line 10).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the maleic anhydride copolymers of Tonge et al to include the hydrophobic esters of Maeda et al because Tonge et al and Maeda et al teach it is within the ordinary skill in the art to use maleic anhydride-based copolymers for the delivery of macromolecules to cells.

One would have been motivated to make such a modification in order to receive the expected benefit of being able to deliver the complex as a water soluble composition while maintaining the lipid solubility of the maleic anhydride-based copolymer as taught by Maeda et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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